

CLIMARA - estradiol patch

Bayer HealthCare Pharmaceuticals Inc.

PRESCRIBING INFORMATION

Rx only

Warnings

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

There is no evidence that the use of “natural” estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses. (See WARNINGS, Malignant neoplasms, Endometrial cancer.)

CARDIOVASCULAR AND OTHER RISKS

Estrogens with and without progestins should not be used for the prevention of cardiovascular disease or dementia. (See WARNINGS, Cardiovascular disorders and Dementia.)

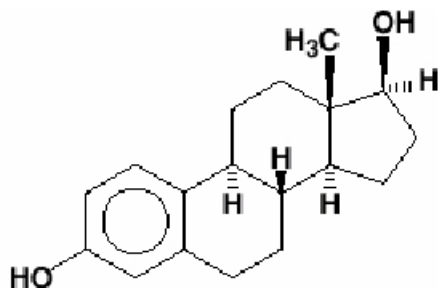
The Women’s Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5mg) relative to placebo. (See CLINICAL PHARMACOLOGY, Clinical Studies and WARNINGS, Cardiovascular disorders and Malignant neoplasms, Breast cancer.)

The Women’s Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See CLINICAL PHARMACOLOGY, Clinical Studies and WARNINGS, Dementia and PRECAUTIONS, Geriatric Use.)

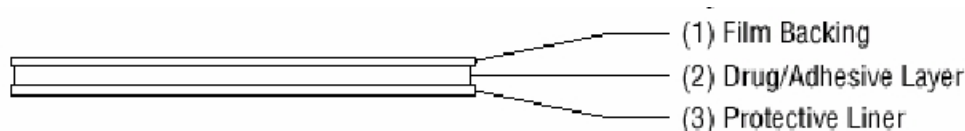
Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

Climara[®], estradiol transdermal system, is designed to release estradiol continuously upon application to intact skin. Six (6.5, 9.375, 12.5, 15, 18.75 and 25 cm²) systems are available to provide nominal *in vivo* delivery of 0.025, 0.0375, 0.05, 0.06, 0.075 or 0.1 mg respectively of estradiol per day. The period of use is 7 days. Each system has a contact surface area of either 6.5, 9.375, 12.5, 15, 18.75 or 25 cm², and contains 2, 2.85, 3.8, 4.55, 5.7 or 7.6 mg of estradiol USP respectively. The composition of the systems per unit area is identical. Estradiol USP is a white, crystalline powder, chemically described as estra-1,3,5(10)-triene-3, 17 β -diol. It has an empirical formula of C₁₈H₂₄O₂ and molecular weight of 272.39. The structural formula is:



The Climara system comprises three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyethylene film, and (2) an acrylate adhesive matrix containing estradiol USP. A protective liner (3) of siliconized or fluoropolymer-coated polyester film is attached to the adhesive surface and must be removed before the system can be used.



The active component of the system is estradiol. The remaining components of the system (acrylate copolymer adhesive, fatty acid esters, and polyethylene backing) are pharmacologically inactive.

CLINICAL PHARMACOLOGY

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol at the receptor level. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

Pharmacokinetics

Transdermal administration of Climara produces mean serum concentrations of estradiol comparable to those produced by premenopausal women in the early follicular phase of the ovulatory cycle. The pharmacokinetics of estradiol following application of the Climara system were investigated in 197 healthy postmenopausal women in six studies. In five of the studies Climara system was applied to the abdomen and in a sixth study application to the buttocks and abdomen were compared.

Absorption

The Climara transdermal delivery system continuously releases estradiol which is transported across intact skin leading to sustained circulating levels of estradiol during a 7-day treatment period. The systemic availability of estradiol after transdermal administration is about 20 times higher than that after oral administration. This difference is due to the absence of first pass metabolism when estradiol is given by the transdermal route.

In a bioavailability study, the Climara 6.5 cm² was studied with the Climara 12.5 cm² as reference. The mean estradiol levels in serum from the two sizes are shown in Figure 1.

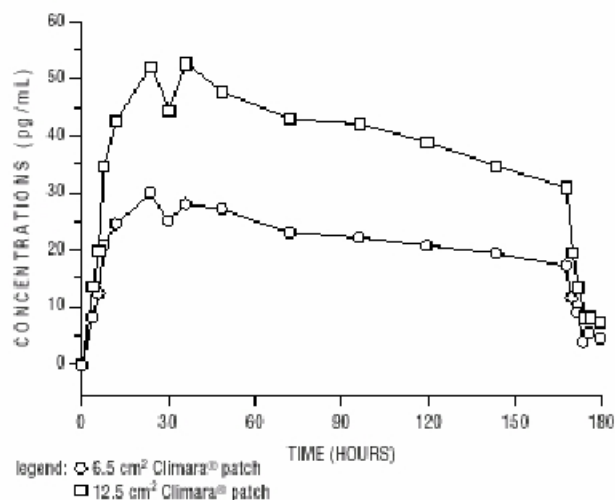


Figure 1: Mean Serum 17β-Estradiol Concentrations vs. Time Profile following Application of a 6.5 cm² Transdermal Patch and Application of a 12.5 cm² Climara patch

Dose proportionality was demonstrated for the Climara 6.5 cm² transdermal system as compared to the Climara 12.5 cm² transdermal system in a 2-week crossover study with a 1-week washout period between the two-transdermal systems in 24 postmenopausal women.

Dose proportionality was also demonstrated for the Climara system (12.5 cm² and 25 cm²) in a 1-week study conducted in 54 postmenopausal women. The mean steady state levels (C_{avg}) of the estradiol during the application of Climara 25 cm² and 12.5 cm² on the abdomen were about 80 and 40 pg/mL, respectively.

In a 3 week multiple application study in 24 postmenopausal women, the 25 cm² Climara system produced average peak estradiol concentrations (Cmax) of approximately 100 pg/mL. Trough values at the end of each wear interval (Cmin) were approximately 35 pg/mL. Nearly identical serum curves were seen each week, indicating little or no accumulation of estradiol in the body. Serum estrone peak and trough levels were 60 and 40 pg/mL, respectively.

In a single dose, randomized, crossover study conducted to compare the effect of site of application, 38 postmenopausal women wore a single Climara 25 cm² system for 1 week on the abdomen and buttocks. The estradiol serum concentration profiles are shown in Figure 2. Cmax and Cavg values were, respectively, 25% and 17% higher with the buttock application than with the abdomen application.

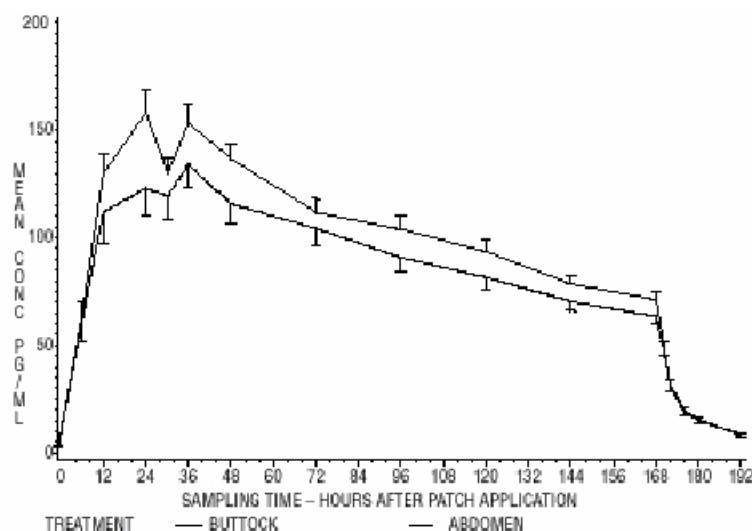


Figure 2: Observed Mean (\pm S.E.) Estradiol Serum Concentrations for a One Week Application of the Climara® system (25 cm²) to the abdomen and buttocks of 38 postmenopausal women

Table 1 provides a summary of estradiol pharmacokinetic parameters determined during evaluation of Climara.

Table 1: Pharmacokinetic Summary (Mean Estradiol Values)

| Climara Delivery Rate | Surface Area (cm ²) | Application Site | No. of Subjects | Dosing | Cmax (pg/mL) | Cmin (pg/mL) | Cavg (pg/mL) |
|-----------------------|---------------------------------|------------------|-----------------|--------|--------------|--------------|--------------|
| 0.025 | 6.5 | Abdomen | 24 | Single | 32 | 17 | 22 |
| 0.05 | 12.5 | Abdomen | 102 | Single | 71 | 29 | 41 |
| 0.1 | 25 | Abdomen | 139 | Single | 147 | 60 | 87 |
| 0.1 | 25 | Buttock | 38 | Single | 174 | 71 | 106 |

The relative standard deviation of each pharmacokinetic parameter after application to the abdomen averaged 50%, which is indicative of the considerable intersubject variability associated with transdermal drug delivery. The relative standard deviation of each pharmacokinetic parameter after application to the buttock was lower than that after application to the abdomen (e.g., for Cmax 39% vs 62%, and for Cavg 35% vs 48%).

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens.

Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to

estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant proportion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

Special Populations

Geriatric:

There have not been sufficient numbers of geriatric patients involved in clinical studies utilizing Climara to determine whether those over 65 years of age differ from younger subjects in their response to Climara.

Pediatric:

No pharmacokinetic study for Climara has been conducted in a pediatric population.

Gender:

Climara is indicated for use in women only.

Race:

No studies were done to determine the effect of race on the pharmacokinetics of Climara.

Patients with Renal Impairment:

Total estradiol serum levels are higher in postmenopausal women with end stage renal disease (ESRD) receiving maintenance hemodialysis than in normal subjects at baseline and following oral doses of estradiol. Therefore, conventional transdermal estradiol doses used in individuals with normal renal function may be excessive for postmenopausal women with ESRD receiving maintenance hemodialysis.

Patients with Hepatic Impairment:

Estrogens may be poorly metabolized in patients with impaired liver function and should be administered with caution.

Drug Interactions

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (*Hypericum perforatum*), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

Adhesion

An open-label study of adhesion potentials of placebo transdermal systems that correspond to the 6.5 cm² and 12.5 cm² sizes of Climara was conducted in 112 healthy women of 45-75 years of age. Each woman applied both transdermal systems weekly, on the upper outer abdomen, for 3 consecutive weeks. It should be noted that lower abdomen and upper quadrant of the buttock are the approved sites of application for Climara.

The adhesion assessment was done visually on Days 2, 4, 5, 6, 7 of each week of transdermal system wear. A total of 1654 adhesion observations were conducted for 333 transdermal systems of each size.

Of these observations, approximately 90% showed essentially no lift for both the 6.5 cm² and 12.5 cm² transdermal systems. Of the total number of transdermal systems applied, approximately 5% showed complete detachment for each size. Adhesion potentials of the 18.75 cm² and 25 cm² sizes of transdermal systems (0.075 mg/day and 0.1 mg/day) have not been studied.

Clinical Studies

Effects on vasomotor symptoms

A study of 214 women 25 to 74 years old met the qualification criteria and were randomly assigned to one of the three treatment groups: 72 to the 0.05 mg estradiol patch, 70 to the 0.1 mg estradiol patch, and 72 to placebo. Potential subjects were postmenopausal women in good general health who experienced vasomotor symptoms. Natural menopause patients had not menstruated for at least 12 months and surgical menopause patients had undergone bilateral oophorectomy at least 4 weeks before evaluation for study entry. In order to enter the 11-week treatment phase of the study, potential subjects must have experienced a minimum of five moderate to

severe hot flushes per week, or a minimum of 15 hot flushes of any severity per week, for 2 consecutive weeks. Women wore the patches in a cyclical fashion (three weeks on and one week off).

During treatment, all subjects used diaries to record the number and severity of hot flushes. Subjects were monitored by clinic visits at the end of weeks 1, 3, 7, and 11 and by telephone at the end of weeks 4, 5, 8, and 9.

Adequate data for the analysis of efficacy was available from 191 subjects. The results are presented as the mean \pm SD number of flushes in each of the 3 treatment weeks of each 4-week cycle. In the 0.05 mg estradiol group, the mean weekly hot flush rate across all treatment cycles decreased from 46 ± 6.5 at baseline to 20 ± 3 (-67%). The 0.1 mg estradiol group had a decline in the mean weekly hot flush rate from 52 ± 4.4 at baseline to 16 ± 2.4 (-72%). In the placebo group, the mean weekly hot flush rate declined from 53 ± 4.5 at baseline to 46 ± 6.5 (-18.1%). Compared with placebo, the 0.05 mg and 0.1 mg estradiol groups showed a statistically significantly larger mean decrease in hot flushes across all treatment cycles ($P < 0.05$). When the response to treatment was analyzed for each of the three cycles of therapy, similar statistically significant differences were observed between both estradiol treatment groups and the placebo group during all treatment cycles.

In a double-blind, placebo-controlled, randomized study of 187 women receiving Climara 0.025 mg/day or placebo continuously for up to three 28-day cycles, the Climara 0.025 mg/day dosage was shown to be statistically better than placebo at weeks 4 and 12 for relief of both the frequency and severity of moderate-to-severe vasomotor symptoms.

Table 2: Mean Change from Baseline in the Number of Moderate-to-Severe Vasomotor Symptoms (ITT)

| Treatment Group | Statistics | Week 4 | Week 8 | Week 12 |
|--------------------|------------|--------|--------|---------|
| E ₂ TDS | N | 82 | 84 | 68 |
| | Mean | -6.45 | -7.69 | -7.56 |
| | SD | 4.65 | 4.76 | 4.64 |
| Placebo | N | 83 | 71 | 65 |
| | Mean | -5.11 | -5.98 | -5.98 |
| | SD | 7.43 | 8.63 | 9.69 |
| | p-Value | <0.002 | | <0.003 |

A second active-control trial of 193 randomized subjects was supportive of the placebo-controlled trial.

Effects on bone mineral density

A two-year clinical trial enrolled a total of 175 healthy, hysterectomized, postmenopausal, non-osteoporotic (i.e., lumbar spine bone mineral density > 0.9 gm/cm²) women at 10 study centers in the United States. 129 subjects were allocated to receive active treatment with 4 different doses of estradiol patches (6.5, 12.5, 15, 25 cm²) and 46 subjects were allocated to receive placebo patches. 77% of the randomized subjects (100 on active drug and 34 on placebo) contributed data to the analysis of percent change of A-P spine bone mineral density (BMD), the primary efficacy variable (see Figure 3). A statistically significant overall treatment effect at each timepoint was noted, implying bone preservation for all active treatment groups at all timepoints, as opposed to bone loss for placebo at all timepoints.

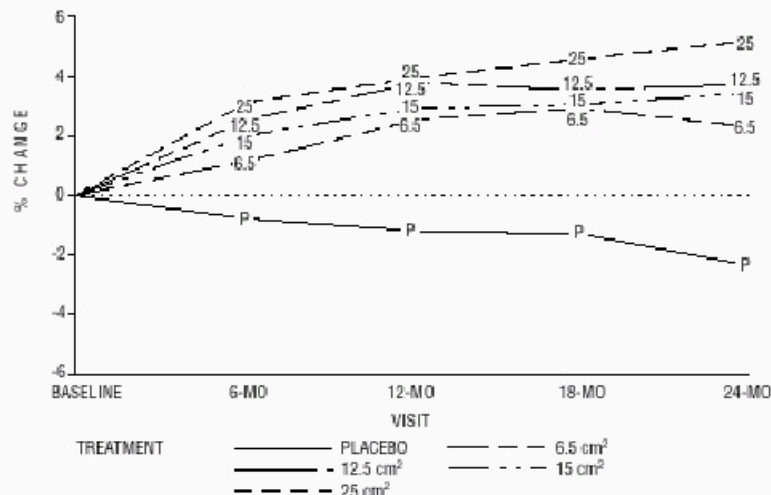


Figure 3: Mean Percent Change from Baseline in Lumbar Spine (A-P View) Bone Mineral Density By Treatment and Time last observation carried forward**

Percent change in BMD of the total hip (see Figure 4) was also statistically significantly different from placebo for all active treatment groups. The results of the measurements of biochemical markers supported the finding of efficacy for all doses of transdermal estradiol. Serum osteocalcin levels decreased, indicative of a decrease in bone formation, at all timepoints for all active treatment doses, statistically significantly different from placebo (which generally rose). Urinary deoxypyridinoline and pyridinoline changes also suggested a decrease in bone turnover for all active treatment groups.

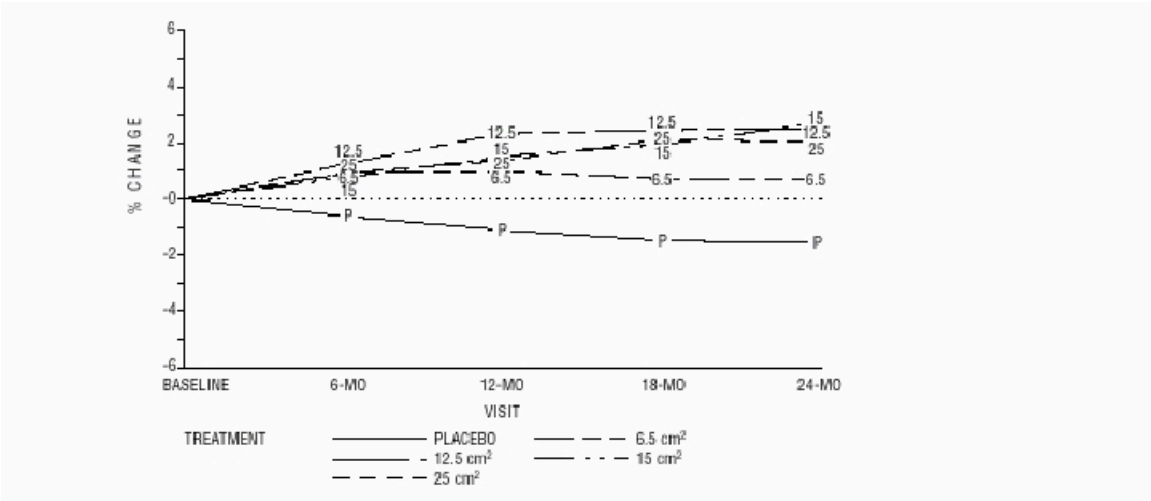


Figure 4 Mean Percent Change from Baseline in Total Hip by Treatment and Time* last observation carried forward** Footnote: This figure is based on 74% of the randomized subjects (95 on active drug and 34 on placebo).

Women's Health Initiative Studies

The Women's Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of either the use of oral 0.625 mg conjugated estrogens (CE) per day alone or the use of 0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate (MPA) per day compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PB), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of CE or CE/MPA on menopausal symptoms.

The CE/MPA substudy was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." Results of the CE/MPA substudy, which included 16,608 women (average age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, 5.5% Hispanic), after an average follow-up of 5.2 years are presented in Table 3 below:

Table 3 Relative and Absolute Risk Seen in the CE/MPA Substudy of WHI*

| Event ^c | Relative Risk CE/MPA vs placebo at 5.2 Years (95% CI [†]) | Placebo n = 8102 | CE/MPA n = 8506 |
|-------------------------------------|--|---------------------------------------|--------------------|
| | | Absolute Risk per 10,000 Person-years | |
| CHD events | 1.29 (1.02-1.63) | 30 | 37 |
| Non-fatal MI | 1.32 (1.02-1.72) | 23 | 30 |
| CHD death | 1.18 (0.70-1.97) | 6 | 7 |
| Invasive breast cancer [‡] | 1.26 (1.00-1.59) | 30 | 38 |
| Stroke | 1.41 (1.07-1.85) | 21 | 29 |
| Pulmonary embolism | 2.13 (1.39-3.25) | 8 | 16 |

| | | | |
|---|------------------|-----|-----|
| Colorectal cancer | 0.63 (0.43-0.92) | 16 | 10 |
| Endometrial cancer | 0.83 (0.47-1.47) | 6 | 5 |
| Hip fracture | 0.66 (0.45-0.98) | 15 | 10 |
| Death due to causes other than the events above | 0.92 (0.74-1.14) | 40 | 37 |
| Global Index [§] | 1.15 (1.03-1.28) | 151 | 170 |
| Deep vein thrombosis [¶] | 2.07 (1.49-2.87) | 13 | 26 |
| Vertebral fractures [¶] | 0.66 (0.44-0.98) | 15 | 9 |
| Other osteoporotic fractures [¶] | 0.77 (0.69-0.86) | 170 | 131 |

*adapted from JAMA, 2002; 288:321-333

† nominal confidence intervals unadjusted for multiple looks and multiple comparisons

‡ includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer

§ a subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes

¶ not included in Global Index

For those outcomes included in the "global index," the absolute excess risks per 10,000 women-years in the group treated with CE/MPA were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (See Boxed Warnings, WARNINGS, and PRECAUTIONS .).

Women's Health Initiative Memory Study

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, enrolled 4,532 predominantly postmenopausal women 65 years of age and older (47% were age 65 to 69 years, 35% were 70 to 74 years, and 18% were 75 years of age and older) to evaluate the effects of CE/MPA (0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate) on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 4 years, 40 women in the estrogen/progestin group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95% CI, 1.21 to 3.48) compared to placebo. Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women. (See Boxed Warnings and WARNINGS, Dementia and PRECAUTIONS , Geriatric use.)

INDICATIONS AND USAGE

Climara is indicated in the:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.
4. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

The mainstays for decreasing the risk of postmenopausal osteoporosis are weight bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacologic therapy. Postmenopausal women require an average of 1500 mg/day of elemental calcium. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake. Vitamin D supplementation of 400-800 IU/day may also be required to ensure adequate daily intake in postmenopausal women.

CONTRAINDICATIONS

Climara should not be used in women with any of the following conditions:

1. Undiagnosed abnormal genital bleeding.
2. Known, suspected, or history of cancer of the breast.
3. Known or suspected estrogen-dependent neoplasia.

4. Active deep vein thrombosis, pulmonary embolism or a history of these conditions.
5. Active or recent (e.g. within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).
6. Liver dysfunction or disease.
7. Climara should not be used in patients with known hypersensitivity to its ingredients.
8. Known or suspected pregnancy. There is no indication for Climara in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy (see PRECAUTIONS).

WARNINGS

See Boxed Warnings.

1. Cardiovascular disorders

Estrogen and estrogen/progestin therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogens should be discontinued immediately.

Risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (e.g., personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

a. Coronary heart disease and stroke

In the Women's Health Initiative (WHI) study, an increased risk of stroke was observed in women receiving oral CE compared to placebo.

In the CE/MPA substudy of WHI an increased risk of coronary heart disease (CHD) events (defined as non-fatal myocardial infarction and CHD death) was observed in women receiving CE/MPA compared to women receiving placebo (37 vs 30 per 10,000 women years). The increase in risk was observed in year one and persisted. (See CLINICAL PHARMACOLOGY, Clinical Studies.)

In the same substudy of WHI, an increased risk of stroke was observed in women receiving CE/MPA compared to women receiving placebo (29 vs 21 per 10,000 women-years). The increase in risk was observed after the first year and persisted.

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS) treatment with CE/MPA (0.625mg/2.5mg per day) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE/MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred and twenty one women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE/MPA group and the placebo group in HERS, HERS II, and overall.

b. Venous thromboembolism (VTE)

In the Women's Health Initiative (WHI) study, an increased risk of deep vein thrombosis was observed in women receiving CE compared to placebo.

In the CE/MPA substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the CE/MPA group compared to 16 per 10,000 women-years in the placebo group. The increase in VTE risk was observed during the first year and persisted. (See CLINICAL PHARMACOLOGY, Clinical Studies .)

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

2. Malignant neoplasms

a. Endometrial cancer

The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of

estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

b. Breast cancer

The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) substudy of CE/MPA (see CLINICAL PHARMACOLOGY, Clinical Studies). The results from observational studies are generally consistent with those of the WHI clinical trial and report no significant variation in the risk of breast cancer among different estrogens or progestins, doses, or routes of administration.

The CE/MPA substudy of WHI reported an increased risk of breast cancer in women who took CE/MPA for a mean follow-up of 5.6 years. Observational studies have also reported an increased risk for estrogen/progestin combination therapy, and a smaller increased risk for estrogen alone therapy, after several years of use. In the WHI trial and from observational studies, the excess risk increased with duration of use. From observational studies, the risk appeared to return to baseline in about five years after stopping treatment. In addition, observational studies suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen/progestin combination therapy as compared to estrogen alone therapy.

In the CE/MPA substudy, 26% of the women reported prior use of estrogen alone and/or estrogen/progestin combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01-1.54), and the overall absolute risk was 41 vs. 33 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 vs. 25 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 vs. 36 cases per 10,000 women-years for CE/MPA compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE/MPA group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

3. Dementia

In the Women's Health Initiative Memory Study (WHIMS), 4,532 generally healthy postmenopausal women 65 years of age and older were studied, of whom 35% were 70 to 74 years of age and 18% were 75 or older. After an average follow-up of 4 years, 40 women being treated with CE/MPA (1.8%, n=2,229) and 21 women in the placebo group (0.9%, n=2,303) received diagnoses of probable dementia. The relative risk for CE/MPA versus placebo was 2.05 (95% confidence interval 1.21 - 3.48), and was similar for women with and without histories of menopausal hormone use before WHIMS. The absolute risk of probable dementia for CE/MPA versus placebo was 45 versus 22 cases per 10,000 women-years, and the absolute excess risk for CE/MPA was 23 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See CLINICAL PHARMACOLOGY, Clinical Studies and PRECAUTIONS , Geriatric use.)

4. Gallbladder disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

5. Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

6. Visual abnormalities

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

PRECAUTIONS

A. General

1. Addition of a progestin when a woman has not had a hysterectomy.

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone.

Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone treatment. These include a possible increased risk of breast cancer.

2. Elevated blood pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

3. Hypertriglyceridemia

In patients with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

4. Impaired liver function and past history of cholestatic jaundice

Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

5. Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T₄ and T₃ serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

6. Fluid retention

Because estrogens may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

7. Hypocalcemia

Estrogens should be used with caution in individuals with severe hypocalcemia.

8. Ovarian cancer

The CE/MPA sub-study of WHI reported that estrogen plus progestin increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE/MPA versus placebo was 1.58 (95% confidence interval 0.77-3.24) but was not statistically significant. The absolute risk for CE/MPA versus placebo was 4.2 versus 2.7 cases per 10,000 women-years. In some epidemiological studies, the use of estrogen alone, in particular for ten or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

9. Exacerbation of endometriosis

Endometriosis may be exacerbated with administration of estrogens. A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen alone therapy. For patients known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

10. Exacerbation of other conditions

Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

In women with hereditary angioderma, exogenous estrogens may induce or exacerbate symptoms of angioderma.

B. PATIENT INFORMATION

Physicians are advised to discuss the PATIENT INFORMATION leaflet with patients for whom they prescribe Climara.

C. LABORATORY TESTS

Estrogen administration should be initiated at the lowest dose approved for the indication and then guided by clinical response rather than by serum hormone levels (e.g. estradiol, FSH).

D. DRUG/LABORATORY TEST INTERACTIONS

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
2. Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T₄ levels (by column or by radioimmunoassay) or T₃ levels by radioimmunoassay. T₃ resin uptake is decreased, reflecting the elevated TBG. Free T₄ and free T₃ concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.
3. Other binding proteins may be elevated in serum (i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG)) leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I-antitrypsin, ceruloplasmin).
4. Increased plasma HDL and HDL₂ cholesterol subfraction concentrations, reduced LDL cholesterol concentration, and in oral formulations increased triglyceride levels.
5. Impaired glucose tolerance.
6. Reduced response to metyrapone test.

E. CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term continuous administration of estrogen, with and without progestin, in women with and without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer. (See Boxed Warnings, WARNINGS and PRECAUTIONS .) Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

F. PREGNANCY

Climara should not be used during pregnancy. (See CONTRAINDICATIONS .)

G. NURSING MOTHERS

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving this drug. Caution should be exercised when Climara is administered to a nursing woman.

H. PEDIATRIC USE

Estrogen replacement therapy has been used for the induction of puberty in adolescents with some forms of pubertal delay. Safety and effectiveness in pediatric patients have not otherwise been established. Large and repeated doses of estrogen over an extended time period have been shown to accelerate epiphyseal closure, which could result in short adult stature if treatment is initiated before the completion of physiologic puberty in normally developing children. If estrogen is administered to patients whose bone growth is not complete, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended during estrogen administration. Estrogen treatment of prepubertal girls also induces premature breast development and vaginal cornification, and may induce vaginal bleeding. In boys, estrogen treatment may modify the normal pubertal process and induce gynecomastia. (See INDICATIONS AND USAGE and Dosage and Administration.)

I. GERIATRIC USE

There have not been sufficient numbers of geriatric patients involved in clinical studies utilizing Climara to determine whether those over 65 years of age differ from younger subjects in their response to Climara.

In the Women's Health Initiative Memory Study, including 4,532 women 65 years of age and older, followed for an average of 4 years, 82% (n=3,729) were 65 to 74 while 18% (n=803) were 75 and over. Most women (80%) had no prior hormone therapy use. Women treated with conjugated estrogens plus medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia. Alzheimer's disease was the most common classification of probable dementia in both the conjugated estrogens plus medroxyprogesterone acetate group and the placebo group. Ninety percent of the cases of probable dementia occurred in the 54% of women that were older than 70. (See Boxed Warnings and WARNINGS, Dementia .)

ADVERSE REACTIONS

See Boxed Warnings, WARNINGS and PRECAUTIONS .

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Summary of Most Frequently Reported Adverse Experiences/Medical Events (≥5%) by Treatment Groups

| | Climara | | | |
|---------------------------------|---------------------------------|--------------------------------|--------------------------|---------------------------|
| AE per Body System | 0.025 mg/day (N=219) | 0.05 mg/day (N=201) | 0.1 mg/day(N=194) | Placebo (N=72) |
| <u>Body as a Whole</u> Headache | 21% | 39% | 37% | 29% |
| Pain | 5% | 18% | 13% | 10% |
| Back Pain | 1% | 8% | 11% | 7% |
| Edema | 4% | 8% | 9% | 6% |
| | 0.5% | 13% | 10% | 6% |
| <u>Gastro-Intestinal</u> | 9% | 21% | 29% | 18% |
| Abdominal Pain | 0% | 11% | 16% | 8% |
| Nausea | 1% | 5% | 6% | 3% |
| Flatulence | 1% | 3% | 7% | 1% |
| <u>Musculo-Skeletal</u> | 7% | 9% | 11% | 4% |
| Arthralgia | 1% | 5% | 5% | 3% |
| <u>Psychiatric</u> | 13% | 10% | 11% | 1% |
| Depression | 1% | 5% | 8% | 0% |
| <u>Reproductive</u> | 12% | 18% | 41% | 11% |
| Breast Pain | 5% | 8% | 29% | 4% |
| Leukorrhea | 1% | 6% | 7% | 1% |
| <u>Respiratory</u> | 15% | 26% | 29% | 14% |
| URTI | 6% | 17% | 17% | 8% |
| Pharyngitis | 0.5% | 3% | 7% | 3% |
| Sinusitis | 4% | 4% | 5% | 3% |
| Rhinitis | 2% | 4% | 6% | 1% |
| <u>Skin and Appendages</u> | 19% | 12% | 12% | 15% |
| Pruritus | 0.5% | 6% | 3% | 6% |

Postmarketing Experience: The following adverse reactions have been identified during post approval use of Climara: a few cases in which there were a combination of the symptoms of generalized hives or rash with swelling of the throat or eyelid edema. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following additional adverse reactions have been reported with estrogen and/or progestin therapy.

1. Genitourinary system

Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding; spotting; dysmenorrhea; increase in size of uterine leiomyomata; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer.

2. Breasts

Tenderness, enlargement, pain, nipple discharge, galactorrhea; fibrocystic breast changes; breast cancer.

3. Cardiovascular

Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure.

4. Gastrointestinal

Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; increased incidence of gall bladder disease; pancreatitis; enlargement of hepatic hemangiomas.

5. Skin

Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; pruritus, rash.

6. Eyes

Retinal vascular thrombosis, intolerance to contact lenses.

7. Central nervous system

Headache; migraine; dizziness; mental depression; chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy, dementia.

8. Miscellaneous

Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthralgias; leg cramps; changes in libido; anaphylactoid/anaphylactic reactions; hypocalcemia; exacerbation of asthma; increased triglycerides.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing oral contraceptives by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

When estrogen is prescribed for a postmenopausal woman with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. Use of estrogen, alone or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (e.g., 3-month to 6-month intervals) to determine if treatment is still necessary (See Boxed Warnings and WARNINGS.) For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

Patients should be started at the lowest dose. Six (6.5, 9.375, 12.5, 15, 18.75 and 25 cm²) Climara systems are available. For the treatment of vasomotor symptoms, treatment should be initiated with the 6.5 cm² (0.025 mg/day) Climara system applied to the skin once weekly. The dose should be adjusted as necessary to control symptoms. Clinical responses (relief of symptoms) at the lowest effective dose should be the guide for establishing administration of the Climara system, especially in women with an intact uterus. Attempts to taper or discontinue the medication should be made at 3- to 6-month intervals. In women who are not currently taking oral estrogens, treatment with the Climara system can be initiated at once. In women who are currently taking oral estrogen, treatment with the Climara system can be initiated 1-week after withdrawal of oral therapy or sooner if symptoms reappear in less than 1-week. For the prevention of postmenopausal osteoporosis, the minimum dose that has been shown to be effective is the 6.5 cm² (0.025 mg/day) Climara system. Response to therapy can be assessed by biochemical markers and measurement of bone mineral density.

Application of the System

The adhesive side of the Climara system should be placed on a clean, dry area of the lower abdomen or the upper quadrant of the buttock. **The Climara system should not be applied to or near the breasts.** The sites of application must be rotated, with an interval of at least 1-week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. The waistline should be avoided, since tight clothing may rub and remove the system. Application to areas where sitting would dislodge the system should also be avoided. The system should be applied immediately after opening the pouch and removing the protective liner. The system should be pressed firmly in place with the fingers for about 10 seconds, making sure there is good contact, especially around the edges. If the system lifts, apply pressure to maintain adhesion. In the event that a system should fall off, a new system should be applied for the remainder of the 7-day dosing interval. Only one system should be worn at any one time during the 7-day dosing interval. Swimming, bathing, or using a sauna while using the Climara system has not been studied, and these activities may decrease the adhesion of the system and the delivery of estradiol.

Removal of the System

Removal of the system should be done carefully and slowly to avoid irritation of the skin. Should any adhesive remain on the skin after removal of the system, allow the area to dry for 15 minutes. Then gently rubbing the area with an oil-based cream or lotion should remove the adhesive residue.

Used patches still contain some active hormones. Each patch should be carefully folded in half so that it sticks to itself before throwing it away.

HOW SUPPLIED

| | |
|--|------------------|
| Climara (estradiol transdermal system), 0.025 mg/day — each 6.5 cm ² system contains 2 mg of estradiol USP | NDC 50419-454-04 |
|--|------------------|

| | |
|--|------------------|
| Individual Carton of 4 systems | |
| Climara (estradiol transdermal system), 0.0375 mg/day — each 9.375 cm ² system contains 2.85 mg of estradiol USP | NDC 50419-456-04 |
| Individual Carton of 4 systems | |
| Climara (estradiol transdermal system), 0.05 mg/day — each 12.5 cm ² system contains 3.8 mg of estradiol USP | NDC 50419-451-04 |
| Individual Carton of 4 systems | |
| Climara (estradiol transdermal system), 0.06 mg/day — each 15 cm ² system contains 4.55 mg of estradiol USP | NDC 50419-459-04 |
| Individual Carton of 4 systems | |
| Climara (estradiol transdermal system), 0.075 mg/day — each 18.75 cm ² system contains 5.7 mg of estradiol USP | NDC 50419-453-04 |
| Individual Carton of 4 systems | |
| Climara (estradiol transdermal system), 0.1 mg/day — each 25 cm ² system contains 7.6 mg of estradiol USP | NDC 50419-452-04 |
| Individual Carton of 4 systems | |

Do not store above 86°F (30°C). Do not store unpouched. Apply immediately upon removal from the protective pouch. The following are representative examples of Climara labeling. See the "How Supplied" section for a complete listing of all components.

CLIMARA 0.025 MG TRADE CARTON

NDC 50419-454-04

4 transdermal systems

Climara[®]

(estradiol transdermal system)

0.025 mg/day

Contents: Each 6.5 cm² system contains 2 mg estradiol USP to provide 0.025 mg of estradiol per day. The inactive components are acrylate copolymer adhesive, fatty acid esters, and polyethylene backing.

For transdermal use only.

Keep this and all drugs out of the reach of children.

Rx only



CLIMARA 0.0375 MG TRADE CARTON

NDC 50419-456-04

4 transdermal systems

Climara®
(estradiol transdermal system)

0.025 mg/day

Contents: Each 6.5 cm² system contains 2.85 mg estradiol USP to provide 0.0375 mg of estradiol per day. The inactive components

are acrylate copolymer adhesive, fatty acid esters, and polyethylene backing.

For transdermal use only.

Keep this and all drugs out of the reach of children.

Rx only



PATIENT INFORMATION UPDATED JUNE 2005

Climara®

(estradiol transdermal system)

Read this PATIENT INFORMATION before you start using Climara[®] and read what you get each time you refill Climara. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about Climara (an estrogen hormone)?

- **Estrogens increase the chances of getting cancer of the uterus.**

Report any unusual vaginal bleeding right away while you are taking estrogens. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.

- **Do not use estrogens with or without progestins to prevent heart disease, heart attacks, strokes, or dementia.**

Using estrogens with or without progestins may increase your chances of getting heart attack, strokes, breast cancer, and blood clots. Using estrogens with progestins may increase your risk of dementia. You and your healthcare provider should talk regularly about whether you still need treatment with Climara.

What is Climara?

Climara is a medicine that contains estrogen hormones.

What is Climara used for?

Climara is used after menopause to:

- **reduce moderate to severe hot flashes.** Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 to 55 years old. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes "surgical menopause."

When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden strong feelings of heat and sweating ("hot flashes" or "hot flushes"). In some women, the symptoms are mild, and they will not need estrogens. In other women, symptoms can be more severe. You and your healthcare provider should talk regularly about whether you still need treatment with Climara.

- **treat moderate to severe dryness, itching, and burning in or around the vagina.** You and your healthcare provider should talk regularly about whether you still need treatment with Climara to control these problems. If you use Climara only to treat your dryness, itching, and burning in and around your vagina, talk with your healthcare provider about whether a topical vaginal product would be better for you.

- **treat certain conditions in which a young woman's ovaries do not produce enough estrogen naturally.**

- **help reduce your chances of getting osteoporosis (thin weak bones).**

Osteoporosis from menopause is a thinning of the bones that makes them weaker and easier to break. If you use Climara only to prevent osteoporosis from menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens might be better for you. You and your healthcare provider should talk regularly about whether you should continue with Climara.

Weight-bearing exercise, like walking or running, and taking calcium and vitamin D supplements may also lower your chances of getting postmenopausal osteoporosis. It is important to talk about exercise and supplements with your healthcare provider before starting them.

Who should not use Climara?

Do not start using Climara if you:

- **have unusual vaginal bleeding.**
- **currently have or have had certain cancers.** Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have or had cancer, talk with your healthcare provider about whether you should take Climara.
- **had a stroke or heart attack in the past year.**
- **currently have or have had blood clots.**
- **currently have or have had liver problems.**

- **are allergic to Climara or any of its ingredients.** See the end of this leaflet for a list of ingredients in Climara.
- **think you may be pregnant**

Tell your healthcare provider:

- **if you are breastfeeding.** The hormone in Climara can pass into your milk.
- **about all of your medical problems.** Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), migraine, endometriosis, lupus, problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.
- **about all the medicines you take.** This includes prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how Climara works. Climara may also affect how your other medicines work.
- **if you are going to have surgery or will be on bed rest.** You may need to stop taking estrogens.

How should I use Climara?

Climara is a patch that you wear on your skin. The estrogen in the Climara patch passes through your skin. You must change your Climara patch every 7 days (once a week). See the end of this leaflet for complete instructions on how to use Climara.

1. Start at the lowest dose and talk to your health care provider about how well that dose is working for you.
2. Estrogens should be used at the lowest dose possible for your treatment only as long as needed. You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about the dose you are taking and whether you still need treatment with Climara.

What are the possible side effects of estrogens?

Less common but serious side effects include:

- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Dementia
- Gallbladder disease
- Ovarian cancer

These are some of the warning signs of serious side effects:

- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting

Call your healthcare provider right away if you get any of these warning signs, or any other unusual symptom that concerns you.

Common side effects include:

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps, bloating
- Nausea and vomiting
- Hair loss

Other side effects include:

- High blood pressure
- Liver problems
- High blood sugar
- Fluid retention
- Enlargement of benign tumors of the uterus (“fibroids”)
- Vaginal yeast infection

These are not all the possible side effects of Climara. For more information, ask your healthcare provider or pharmacist.

What can I do to lower my chances of a serious side effect with Climara?

Talk with your healthcare provider regularly about whether you should continue using Climara:

- If you have a uterus, talk to your healthcare provider about whether the addition of a progestin is right for you.
- See your healthcare provider right away if you get vaginal bleeding while using Climara.
- Have a breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.
- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease. Ask your healthcare provider for ways to lower your chances for getting heart disease.

General information about safe and effective use of Climara.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not take Climara for conditions for which it was not prescribed. Do not give Climara to other people, even if they have the same symptoms you have. It may harm them.

Keep Climara out of the reach of children.

This leaflet provides a summary of the most important information about Climara. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about Climara that is written for health professionals. You can get more information by calling the toll free number (1-888-84BAYER).

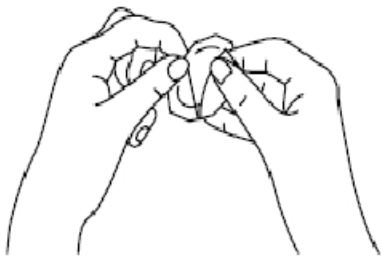
What are the ingredients in Climara?

The active ingredient of Climara is estradiol. Climara also contains acrylate copolymer adhesive, fatty acid esters, and polyethylene backing.

Instructions for Use

How and Where to Apply the Climara Patch

Each Climara patch is individually sealed in a protective pouch. To open the pouch, hold it vertically with the Climara name facing you. Tear off the top of the pouch using the top tear notch. Tear off the side of the pouch using the side tear notch. Pull the pouch open. The Climara patch is the see-through plastic film attached to the clear thicker plastic backing. There is a silver foil-sticker attached to the inside of the pouch. **Do not remove it from the pouch.** The sticker contains a moisture protectant (desiccant). **Lift out the Climara patch.** Notice that the patch is attached to a thicker, hard-plastic backing and that the patch itself is oval and see-through.



Apply the sticky side of the Climara patch to a clean, dry area of the lower stomach below your belly button or the top of the buttocks (see diagram below). **Do not apply the Climara patch to your breasts.** The sites of application on the lower stomach and buttocks must be rotated, allowing at least 1 week between applications to the same site. The site selected should not be oily, damaged, or irritated. Avoid the waistline, since tight clothing may rub and remove the patch. Also, do not put the patch on areas where sitting would rub it off or loosen it. Apply the patch right after opening the pouch and removing the protective liner. Press the patch firmly in place with your fingers for about 10 seconds. Make sure that it sticks all over, especially around the edges.



The Climara patch should be worn continuously for one week. You may wish to try different sites when putting on a new patch, to find ones that are most comfortable for you and where clothing will not rub on the patch or loosen it.

When to Apply the Climara System?

The Climara patch should be changed once weekly. Remove the used patch. Carefully fold it in half so that it sticks to itself because used patches still contain active hormones and discard it. Any adhesive that might remain on your skin can be easily rubbed off. Then place the new Climara patch on a different skin site. (The same skin site should not be used again for at least 1 week after removal of the patch.)

Contact with water when you are bathing, swimming, or showering may affect the patch. If the patch falls off, the same patch may be reapplied to another area of the lower abdomen. Make sure that there is good contact, especially around the edges. If the patch will not stick completely to your skin, put a new patch on a different area of the lower abdomen. Do not apply two patches at the same time.

Estrogens should be used only as long as needed. You and your health care provider should talk regularly (for example, every 3 to 6 months) about whether you still need treatment with Climara.

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